Methodology for a Better Evaluation of the Relation Between Mechanical Strength of Solids and Polymorphic Form

S. KOPP*, C. BEYER*, E. GRAF*, F. KUBEL† AND E. DOELKER

Laboratoire de Pharmacie galénique, Section de Pharmacie, Université de Genève, 30, quai Ernest-Ansermet, CH-1211 Geneva 4,
* Pharmazeutisches Institut der Universität Tübingen, D-7400 Tübingen. † Laboratoire de Cristallographie de l'Université de Genève, 24, quai
Ernest-Ansermet, CH-1211 Geneva 4, Switzerland

Abstract—In order to evaluate the role played by polymorphism in the mechanical strength of solid dosage forms (e.g. compressed tablets) and minimize the influence of other factors (such as compaction force, porosity, particle size, and possibly crystal habit), a melted disc technology was developed. With this technique, tablet-shaped discs of zero porosity were prepared by melting powder and subsequent crystallization in the desired modifications. Taking phenobarbitone as a model drug, different methods were used to get discs of forms I, II and III and the amorphous form. Mechanical properties of the discs were assessed, primarily through their bending strength. The Vickers hardness number was also determined for some specimen discs and monocrystals. Results showed that the amorphous form and form III of phenobarbitone gave the toughest discs and would be therefore the most suitable materials to manufacture coherent tablets. Moreover, the various preparation methods used resulted in discs of different internal structures. Both crystal size and crystal habit significantly affected the physical properties of the tested materials.

Many reports have been published on a possible effect of crystallographic polymorphism on the mechanical strength of tablets (Fell & Newton 1970; Conte et al 1974; Burger 1976a, b; Burger et al 1981; Ramberger et al 1983; Summers et al 1977; Hollenbach et al 1980a,b; Hüttenrauch 1983). These authors prepared tablets by compressing powders, but several additional factors, such as compression force, porosity, moisture content, particle size, crystal habit, and variability in the mechanical test method might have also affected the validity of comparative measurements. It was the aim of this work to establish a methodology to minimize the effect of these factors and partially of the crystal habit, and thereby to show the effect of the polymorphic form. Methods were thus developed to prepare tablet-shaped discs (round or oval) from powders which were melted and subsequently crystallized in the desired modification. These tablet-models are supposed to have zero porosity and therefore maximum apparent density, corresponding to the true density of the substance.

The model drug chosen was phenobarbitone (Phenobarbital), particularly the crystallographic modifications I, II and III and the amorphous form. Bending strength testing was selected as the best technique to examine the mechanical properties of the discs containing either crystalline modifications or the amorphous form.

Materials and Methods

Preparation of discs
Several methods were developed to prepare tablet-shaped discs containing one specific form, so that only the crystal characteristics (polymorphism and habit) became signifi-

Correspondence to: E. Doelker, Laboratoire de Pharmacie galénique, Section de Pharmacie, Université de Genève, 30, quai Ernest-Ansermet, CH-1211 Geneva 4, Switzerland.

cant. To ensure a better comparison, at least two methods were used to prepare each polymorphic form.

Method 1
The first series of discs was prepared by melting the original phenobarbitone substance (Bayer, lot No. Pt 943298) between two horizontal small glass plates, 1 mm apart. The melted substance was then tempered at the specific temperature allowing the direct formation of the desired polymorphic form from the liquid phase (150–160°C for modification I and 130–140°C for modification II). Crystallization was complete after 24 h. Discs of pure modification III could not be obtained by this method.

Method 2
The substance was melted as above and then quickly cooled to room temperature (20°C). The discs obtained were glassy and proved by differential scanning calorimetry (DSC) and X-ray diffraction to be amorphous. They were first stored at room temperature for one day for stabilization. Forms I and II were then obtained by heating the discs for 3 to 4 h at 150–160°C and 130–140°C, respectively. Form III was produced by heating the discs for 45 min at 95–105°C. Thus, in this method the modifications were formed through the amorphous form as an intermediate.

Method 3
As it was not possible to obtain discs of modification III by method 1, they were prepared by storing the amorphous glassy discs at room temperature. Crystallization in the thermodynamically most stable modification III was complete after a few days. The intermediate state between the amorphous form and modification III is shown in Fig. 1.

The form present in each disc was identified by DSC (Perkin-Elmer DSC-4, 1°C min^{-1} heating rate) and X-ray diffraction (Guinier method, Nonius Guinier film camera,
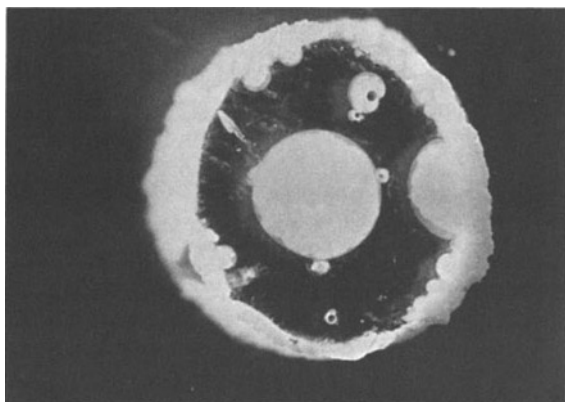
Fig. 1. Photograph of a phenobarbitone disc prepared by method 3 showing the transformation of the amorphous form (transparent area) to modification III (opaque area) (approximate diameter of the discs: 8–12 mm, height about 1 mm).

$CuK_{\bar{a}}$ and $CoK_{\bar{a}}$ radiation, exposure 6 h, calibration with silicium standard). To absorb the fluorescence an aluminium sheet (thickness about 0·05 mm) was placed between the sample and X-ray film.

Preparation of monocrystals

To obtain an even more exact value of the bending strength for one of the material, large crystals of phenobarbitone modification II (Fig. 2) were grown from a saturated ethanolic solution by slow evaporation at room temperature for 3–4 months.

Bending strength

The bending strength of the discs (diameter 8 to 12 mm, height about 1 mm) and of the monocrystals (mean dimensions: $10 \times 20 \times 2$ mm) was determined by an apparatus designed according to the German Industrial Standards (DIN N° 52362, 52112, 51227 and 51230). The maximum force applied to the disc, F, was measured using a piezo-electric transducer (Kistler model 9203, Switzerland) in combination with a charge amplifier (Kistler model 5007) and recorded using an UV oscillograph (Bryan Southern Instruments, UK).

The distance between the fulcrums in each run was always equal to two-thirds of the actual diameter of the disc or the
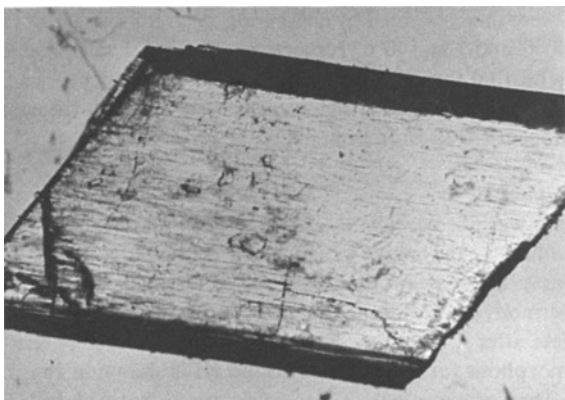

Fig. 2. Photograph of a large crystal of phenobarbitone modification II (approximate size of the tested crystals: $10 \times 20 \times 2$ mm).

length of the monocrystal. According to Müller et al (1976) and Gupte (1977), the calculation of the bending strength, σ, reduces to

$$\sigma = F/t^2 \qquad (1)$$

where t is the thickness of the disc or the monocrystal.

Vickers microhardness

The Vickers surface hardness of discs of the amorphous form, of modification III and of the monocrystals of form II was determined, using a Durimet digital tester (Leitz, W. Germany). The pyramidal indenter was loaded with 10 g. The microhardness was calculated from the measured indentation and load (Gray 1972).

Results and Discussion

Bending strength

Values of bending strength of the discs made from the three modifications, using three different methods, are presented in Table 1. The number of discs tested (n) is specified in each series, together with the standard error of the mean (s.e.m.).

Some dispersion in the results was generally observed, reflecting the difficulty in achieving stable crack propagation in brittle materials. To understand these differences in bending strength, it is necessary to consider the probable internal structure of the specimens.

Modification I, II and III discs

Method 1 (melting-crystallization at specific temperature) produced discs with one dominating crystal growth, observable on the surface (Fig. 3). This is probably due to the fact that one seed crystal, from one point, directs the propagation of further crystallization throughout the whole disc.

An explanation for the scatter in the data can be found in the well known example of quartz. Newnham (1975) showed that the fracture surface energy determined in a breaking test varied greatly depending on the orientation of the crystal planes.

Orientation	Fracture surface energy $(mN\,m^{-1})$
$(11\bar{2}0)$	800
$(10\bar{1}1)$	500
$(10\bar{1}0)$	1000
polycrystalline	4000

Changes in the angle between the cleavage plane and the crystal plane could therefore influence the bending strength

Table 1. Bending strengths $(N\,cm^{-2})$ of discs made of different phenobarbitone modifications (I, II, III).

	I	II	III
Method 1	169 (5;22)*	235 (5;27)	
	171 (6;32)	108 (3;45)	
	113 (7;11)	75 (6;4)	
	133 (3;32)	92 (6;8)	
	66 (5;5)	60 (5;6)	
		83 (8;5)	
		120 (3;10)	
Method 2	71 (7;7)	66 (10;7)	187 (8;13)
	66 (10;3)	82 (8;7)	
Method 3			567 (17;41)

* Number of discs tested and standard error of the mean.

and explain the wide deviation observed. Fracture along a preferential plane gives low values; all other angles produce higher values.

Method 2 (melting—amorphous form—crystallization at specific temperature) produced discs containing smaller crystal agglomerates packed together since many seed crystals develop simultaneously in the solid disc (Fig. 3). Variation in the cleavage angle during the bending test did not result in such differences as in method 1, because first of all there are always some crystallites optimally orientated in the breaking plane and secondly smaller crystals have lower bonding forces between each other.

Method 3 (melting—amorphous form—room temperature) resulted in polycrystalline modification III (Fig. 3). At room temperature the crystallization is slower than at higher temperatures. Thus, more seed crystals are formed, resulting in smaller crystals. These form interlockings homogeneously over the whole discs. These crystal agglomerates were not visible under the microscope. Such a structure can be compared with that of the polycrystalline quartz that needs the highest fracture force.

On comparison of all three modifications and discs, revealed no statistical differences between the mean bending strength values for forms I and II but both of these differed from modification III.

Amorphous form discs

Results for three lots (a) (b) (c) are shown in Table 2.

We presume that the amorphous discs have large glassy 'macrodomains' (Fig. 3) which are randomly developed during the cooling process. No crystallographic breaking plane exists. This explains the high bending strength measured. The high standard error of the mean observed is due to the random distribution of these large 'macrodomains'.

Modification II monocrystals

The mean bending strength of the 19 crystals tested was 187 N cm^{-2} (s.e.m. 9 N cm^{-2}); these monocrystals of modification II were always broken along the same crystallographic plane (Fig. 3). The result is in the same order of magnitude as
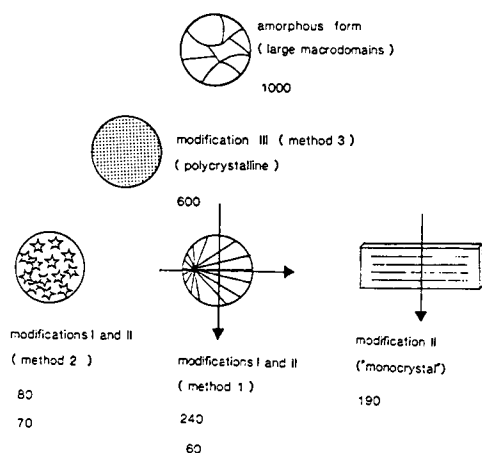

Fig. 3. Schematic representation of the predicted internal structure of discs in relation to their approximate bending strength (N cm^{-2}). For exact values, see Tables 1 and 2.

Table 2. Bending strength (N cm^{-2}) of amorphous phenobarbitone discs.

Lot	Bending strength
a	1006 (16;110)*
b	1187 (13;144)
c	975 (12;139)

* Number of discs tested and standard error of the mean.

Table 3. Vickers hardness numbers of phenobarbitone modifications in comparison with bending strengths.

	Vickers hardness number (N cm^{-2})	Bending strength (N cm^{-2})
Modification III discs ('polycrystalline')	28 000	567
Amorphous form discs	6500	1056
Modification II crystals ('monocrystals')	42 000	187

the highest mean value for the bending strength of discs of form II (Table 1, method 1). Thus the data obtained for the large monocrystals confirm that the proposed disc technique produces specimens which are representative of the material under test and may therefore be used as a model for investigating physical properties of polymorphic substances.

Vickers microhardness

Values for discs of form III (polycrystalline), discs of the amorphous form and monocrystals of form II are presented in Table 3. For the purpose of comparison, bending strengths are also included.

An inverse relationship between surface hardness and bending strength is quite common. Modification II, with the highest Vickers hardness number, showed the lowest bending strength, and the amorphous form, with the lowest hardness, broke at the highest bending force.

Conclusions

Various techniques were used to prepare discs of specific forms of phenobarbitone in order to model the possible effect of polymorphic modification on the mechanical properties of tablets. Model discs produced by different methods demonstrate that, in this case, not only a modification of the polymorphic form tested but, to a greater extent, its crystal habit influences bending strength. This suggests that differences in the failure properties of tablets may not necessarily be a result of crystallographic modification of the particular pharmaceutical substance, but could be due to changes in morphological properties such as crystal habit and particle size. Studies of the behaviour and properties of monocrystals or discs of different crystal modifications could be helpful in characterizing drug compounds which produce unsatisfactory tablets, and could enable modifications with more satisfactory manufacturing properties to be selected.

References

Burger, A. (1976a) Einfluss der Polymorphie des Wirkstoffes auf die Eigenschaften von Tabletten: Chlorpropamid. Part I. Pharm. Ind. 38: 306–312

Burger, A. (1976b) Einfluss der Polymorphie des Wirkstoffes auf die Eigenschaften von Tabletten: Chlorpropamid. Part II. Ibid. 38: 639–643

Burger, A., Ramberger, R., Schmidt, W. (1981) Einfluss der Polymorphie des Wirkstoffes auf die Eigenschaften von Tabletten. 3rd Commun.: Kompressionsverhalten von Meprobamat. Pharmazie 36: 41–46

Conte, U., Colombo, P., Caramella, C., Bettinetti, G. P., Giordano, F., La Manna, A. (1974) On the direct compression of sulfamethoxydiazine (SMD) polymorphic forms—I. Il Farmaco Ed. Prat. 30: 194–206

Fell, J. T., Newton, J. M. (1970) The prediction of the tensile strength of tablets. J. Pharm. Pharmacol. 22: 247–248

Gray, D. E. (1972) American Institute of Physics Handbook, 3rd edition, McGraw Hill Book Co, New York

Gupte, A. R. (1977) Bestimmung der Festigkeit von Presslingen, insbesondere aus dem Biegeversuch. Pharm. Ind. 39: 156–160

Hollenbach, K., Pintye-Hodi, K., Kedvessy, G. (1980a) Zur Poly-

morphie der Barbiturate in Pulvern und Tabletten. 4th Commun.: Auflösung von Barbital B und A (Modifikation I und III) und deren Freisetzung aus Tabletten. Ibid. 35: 32–35

Hollenbach, K., Pintye-Hodi, K., Kedvessy, G. (1980b) Zur Polymorphie der Barbiturate in Pulvern und Tabletten. 5th Commun.: Auflösung umkristallisierter Barbital-Substanzen und Freisetzung aus Tabletten. 35: 95–98

Hüttenrauch, R. (1983) Notiz zur Anwendung der Aktivierungstheorie auf die Tablettenbildung aus polymorphen Substanzen. Pharmazie 38: 198–199

Müller, B. W., Steffens, K. J., List, P. H. (1976) Untersuchungen zur exakten Bestimmung der Bruchfestigkeit von Tabletten. Acta Pharm. Technol. 22: 91–198

Newnham, R. E. (1975) Structure-Property Relations, Springer Verlag, Berlin-New York-Heidelberg

Ramberger, R., Burger, A., Pröll, K. (1983) Einfluss der Polymorphie des Wirkstoffes auf die Eigenschaften von Tabletten. 5th Commun.: Kompressionsverhalten von Sulfathiazol. Sci. Pharm. 51: 198–208

Summers, M. P., Enever, R. P., Carless, J. E. (1977) Influence of Crystal Form on Tensile Strength of Compacts of Pharmaceutical Materials. J. Pharm. Sci. 66: 1172–1175